

Examiner indicates that "Applicant's arguments have been considered but are not found to be persuasive".

The Applicant's arguments to which the Examiner refers are those filed on September 21, 2001 and which are hereafter recalled.

The Examiner relies on the following parts of the disclosure of W0'058, i.e.

- the abstract,
- page 6, l. 13-30
- page 10, l. 21-26
- page 7, l. 15-30 and claim 18
- page 8, l. 1-2 and
- page 17, l. 23-25

Applicants in their communication of September 26, 2001, have shown that the rejection of claim 7 under 35 USC 102(b) as being anticipated by W0'58 is unfounded.

The reasons they set forth were as follows.

Even if, admittedly, W0'058 teaches a method which, according to the Examiner,

"...involves blending the drug with the matrix ingredients, heating the blended mixture, placing the mixture in the extruder, extruding the strands, then dividing the stands into the desired pieces, such as pellets"
(p. 7, l. 15-30, and claim 18).

W0'058 also teaches that

"... a water insoluble retardant, a therapeutically active agent and an optional binder..."(p.17, l.16) are *"....directly meter(ing)ed into an extruder..."* (p.17, l.15).

the *"homogeneous mixture"* (p.17, l.16 and 17) being heated and extruded.

On the contrary, according to new claim 9 the mixture in question is subjected to a maturing step carried out outside the extruder at a temperature from 20 to 70°C

which is maintained at least "30 minutes", advantageously in a ventilated tray type oven before being introduced into the extruding machine inside which it is heated to the extrusion temperature and subjected to the extrusion pressure during 2 to 6 minutes.

W0'058 does not disclose the heating step outside the extruder and therefore the rejection is not well founded.

In the present action the Examiner states that Applicants' arguments are not persuasive, but the Examiner however does not explain why.

Applicants draw the Examiner's attention to the parts of W0'056 which confirm that said reference does not teach a maturation step outside the extruder :

- page 7, lines 15-19 :

"...blending the drup together with all matrix ingredients...."feeding the mixture into an extruder heated to the requisite temperature..."

- page 27, lines 18 to 25 : the successive steps do not comprise a maturing step.

- Figure 9 : no maturing step appears from that figure.

Thus actually a maturing step outside the extruder is not disclosed.

The Examiner urges that

"W0'056 does teach a heating step prior to the extrusion...."and that

"...applicant's claimed maturing steps is simply a heating step with a defined time and temperature..."

However, the examiner has not shown that W0'56 actually discloses such a heating step for which it is specified that it takes place outside the extruder ; and in any case "heating" without maintaining at least 30 minutes would not be maturing and would not produce the effects obtained due to maturing.

The Examiner then disputes the evidence drawn from Examples 1 and 2 and which show that there are a patentable difference between the instant claims and the prior art.

The Examiner states that it is not clear what is being demonstrated by these examples, relying particularly on table I page 15.

Applicants respectfully disagree.

As indicated page 4, line 24 to 31, as well as in new claim 9 the particles obtained after extrusion present an

- -active principale release curve- -

which

- -represents slower kinetics- -

than the particles of same composition extruded immediately without a maturing step, said maturing step consisting in maintaining before extrusion the mixture to be extruded at a temperature from 20 to 70°C during 30 minutes to 150 hours.

The examination of the experimental results collected in Table I shows that the active principale releases slower when increasing the conditions of the maturing step, i.e. duration and temperature; that clearly appears when comparing the release obtained after a two days maturation at 20°C (sample A2) with the release obtained for instance

- after 3 days at 40°C (sample C3)

and

- after 3 days at 70°C (sample B3)

the percentage of released active substance decreasing

- after 0,5 hour from 29,6 (A2) to 9,1 (C3) and to 6.0 (B3)

- after 4 hours from 74,5 (A2) to 55.0 (C3) and to 54.2 (B3).

And that enables the increase the quantity of active substance for a given release curve without increasing the volume of the tablet.

The examiner then states that

"Applicant's added maturing step does not actually require heating..."

However, according to former claim 7 and present claim 9, no heating is contemplated but merely maintaining at a given temperature for a given duration.

Thus the specification contains evidence showing that there actually is a patentable difference between the instant claims and the prior art.

Rejection under 35 USC 103

Claims 7 and 8 were rejected under 35 U.S.C. 103(a) as being unpatentable over W0 96/14058 to Oshlack et al as discussed above, and in view of the following comments.

According to the Examiner, and although

"...W0'058 does not teach that the particles are spheroidal, they do teach the exit port of the extruder can be any shape desired..., the position of the Examiner being that by allowing the exit port of the extruder to be any shape so that the multiparticulates can be of any shape, this allows the exit port to be shape that would form spheroidal particulates".

Applicants who have already addressed that argument respectfully disagree.

The reference does not teach how the shape of the exit port should be .

If the shape of the port could be selected to provide spheroidal particles that would be another invention which is not disclosed in the reference.

And even if the selection were disclosed the solution provided by the instant invention i.e. the particular shape of the blades as claimed in claim 8 which also permits obtaining spheroidal particles, is neither disclosed nor suggested.

Thus the reference is irrelevant and the suppositions the Examiner has drawn from the disclosure are merely unfounded theoretical hypotheses.

Further, again according to the Examiner and

"....although W0'058 does not specifically refer to a maturing step, the Examiner's position is that the heating step prior to extrusion, which is discussed by W0'058, reads on applicant's claimed method".

The Examiner's major argument is that

"there is no evidence to prove that this heating step, discussed by the prior art, takes place inside the extrusion machine."

Applicants respectfully disagree and request the Examiner to consider the

parts of the disclosure of W0'056 hereabove referred to.

Furthermore, absent any precise and clear indication in the reference to the contrary, the latter disclose a conventional extrusion method and extrusion device which is shown on figure 9.

Said figure shows an extrusion device of conventional embodiment in which the heating step of the mixture to be extruded is performed inside the extruder.

With respect to the tool for shopping comprised by the device according to claim 8 the Examiner states that

"It is position of the examiner that the cutting tool claimed by applicant is the equivalent to a typical cutting blade at the exit of the extrusion machine"

However, the Examiner's position is not supported by any showing or evidence.

Consequently, the examiner's argumentation only consists in a series of non supported assumptions.

Thus the rejection under 35 USC 103 cannot be sustained.

In view of the new claim 9 and the foregoing remarks, it appears that Claims 8 and 9 of this application are now in proper form and patentable over the prior art.

Reconsideration and allowance are therefor respectfully solicited.

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,
COHEN & FOKOTILOV, LTD.

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By: 

Alan BERNSTEIN
Registration No. 19,315
1635 Market Street, 12th Floor
Seven Penn Center
Philadelphia, PA 19103-2212
(215) 567-2010
Customer No. 03000
Attorneys for Applicants

CERTIFICATE OF MAILING

I hereby certify that the foregoing Amendment re Application Serial No. 09/402,564, is being deposited with the United States Postal Service as First Class Mail, postage prepaid, in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231, this 2nd day of July, 2002.

A handwritten signature in cursive script, appearing to read "Alan H. Bernstein", written over a horizontal line.

Alan H. Bernstein

ATTACHMENT A (Clean Version)

- 5 8. Apparatus for making particles in the form of spheroids comprising a mixture of an active substance distributed within a thermoplastic material and having a constant diameter in the range from 0.5 to 2mm, said apparatus comprising an extruder which in turn comprises an extrusion die and which is proper to produce extruded filaments of said mixture, said apparatus further comprising, located at the exit of the extrusion die, a tool, for chopping the extruded filaments, wherein said tool is equipped with cutters in the form of blades having a first and second face parallel with one another, the first of which is inclined towards the second, thus forming a cutting edge, the second face being recessed so as to leave a strip of a width of less than 1mm which comprises the cutting edge whereby the shape of the particles obtained by chopping the extruded filaments is directly spheroidal without any additional spheroidal shaping step.
- 10
- 15 9. (Amended) In a method of making particles, in particular spheroids intended to be used for preparing tablets, said particles which include an active substance having a constant diameter in the range from 0.5 mm to 2 mm said method including successively:
- 20 a) - a step of selecting an active substance and a thermoplastic material, including at least one polymer excipient and at least one plasticiser.
- 25 b) – a step of forming a mixture of the active substance and the thermoplastic material,
- c) – a step of introducing the said mixture after maturing into the kneading area of an extruding machine,
- d) – a step of extruding the said mixture, inside the extruding machine comprising a kneading area, without solvent at a controlled temperature to produce at least one extruded filament or extrudate and
- e) – a step of chopping the extruded filament into particles.
- 30 The improvement consisting in providing between steps b) and c) a step of maintaining the mixture of the active substance and of the thermoplastic material at a temperature and for a time respectively selected in the range from 20 to 70C and in the range from 30 minutes to 150 hours causing thus the maturing of the mixture, whereby it becomes possible to store the said mixture for up to 7 days before extruding it, the active principale release curve being stabilized and presenting a kinetics slower than that obtained with particles of

same composition extruded immediately after making up the mixture with no maturing step, due to which the particles obtained by the method including the maturing step of introducing into the organism an increased quantity of active substance for the same or even reduced volume and at an equivalent rate without increasing the volume of a tablet incorporating said particles.